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Synthesis of Antibiotic Linezolid Analogues

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Several new compounds of oxazolidinone class were designed, synthesized and their analogs were evaluated for antibacterial activity against *Staphylococcus aureus*, *Staphylococcus citreus*, *Proteus vulgaris*, *Salmonella typhimurium* and *Klabsiella phenumoniae*. The structures of all the compounds were confirmed by IR, ^{1}H NMR, ^{13}C NMR and mass spectral data.

Key Words: Oxazolidinone, Epichlorohydrin, Antibacterial, Linezolid.

INTRODUCTION

The increasing incidence of bacterial resistance to a large number of antibacterial agents such as β-lactam antibiotics, macrolides, quinolones and vancomycin is becoming a major issue[1-4]. For the past several years, vancomycin has been considered to be the last line of defense against gram-positive infections and there is no suitable therapy available for treating diseases that have become resistant to vancomycin[5].

This growing problem has recently rekindled interest in the search for new antibiotic structural classes that inhibit or kill by novel mechanisms[6]. This encourages the scientists for discovery and development of effective agents against the emerging problematic gram-positive pathogens MRSA, methicillin-resistant coagulase-negative *Staphylococci*, VRE and penicillin-resistant *Pneumococci*, as well as the perceived looming threat of a vancomycin-resistant *Staphylococcus aureus*[7-9]. The oxazolidinones are an important class of molecular architectures found in a broad range of synthetically and biologically interesting compounds. The five membered heterocycles display a broad spectrum of biological activities serving as inhibition of monoamine oxidase[10], HIV-1 inhibitory activity[11], NPCILI ligands[12] and RNA-binding agents[13]. Referring to the structure-activity relationship studies[14-18] and the synthesis of Linzolid[19], we have focused on the synthesis of novel oxazolidinone analogs and evaluated their antibacterial activity.

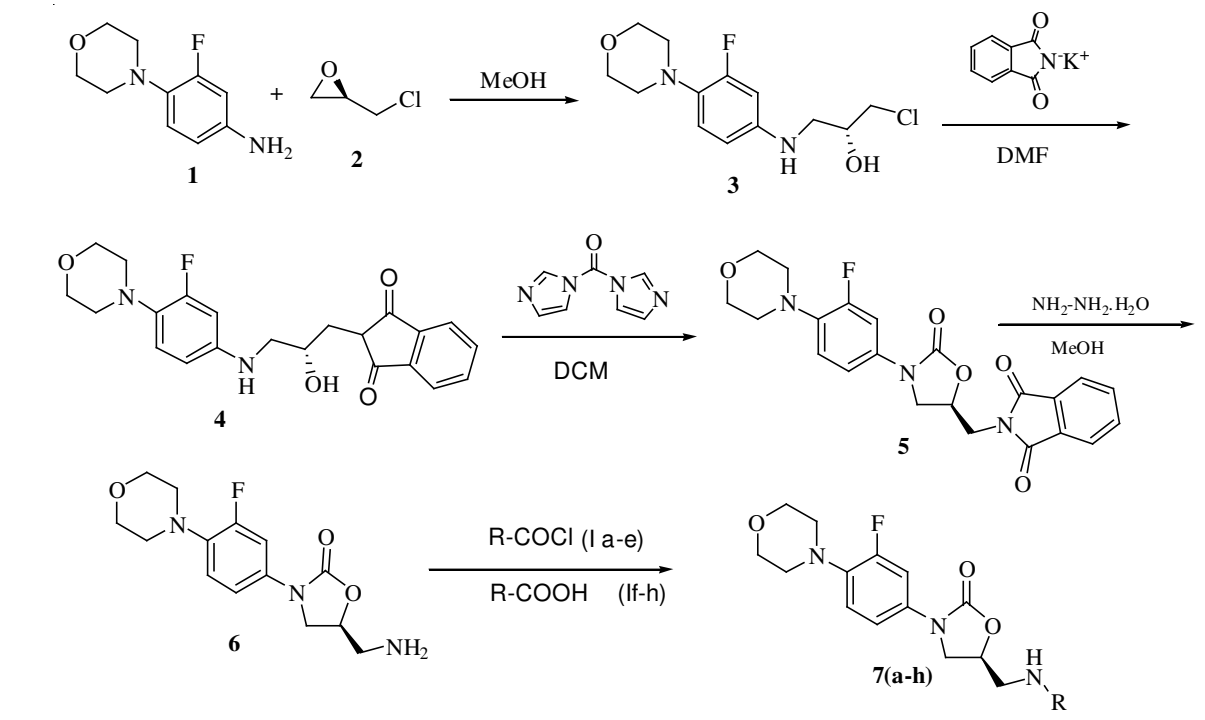
Chemistry: The synthetic route of these compounds is shown in **Schemes I** and **II**. Commencing with 3-fluoro-4-marpholinyl aniline **1** with R-epichlorohydrin **2** selectively gave the N-[3-chloro-2-(R)-hydroxypropyl]-3-fluoro-4-morpholinylaniline **3**. The compound **3** when reacted with potassium pthalamide in DMF gave **4**, which was also prepared from the compound **1**. Compound **1** was treated with (S)-N-2,3-epoxypropyl pthalamide **8** in DMF (**Scheme-II**). Carbonylation of **4** followed by treatment with hydrazine hydrate gave **6**. This sequence of reactions provide directly the (S)-N-{(3-[3-fluoro-4-[4-morpholinyl]-phenyl]-2-oxo-5-oxazolidinyl]-methyl amines **6**. The compound **6** was reacted with corresponding acid chlorides **I(a-e)** and substituted aromatic acids **I(f-h)** to produce linzolid analogs **7(a-h)**. All the compounds synthesized were characterized by IR, ^{1}H NMR, ^{13}C NMR spectrometry and MS.

EXPERIMENTAL

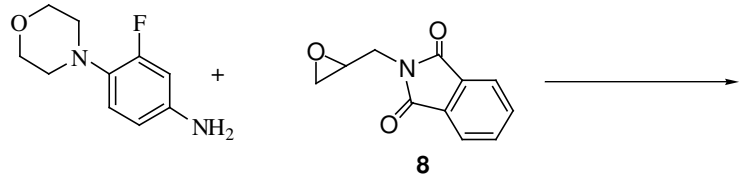
Melting points were determined on Stuart SMP-30 apparatus and are uncorrected. The IR spectra were recorded in the solid state as KBr dispersion media using a Perkin-Elmer model 1600 Fourier transform infrared (FT)-IR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded using a 300-MHz Bruker Avance spectrometer. Chemical shifts values are expressed in δ (ppm) using TMS as the internal standard. The liquid chromatography-mass spectrometry (LC-MS) was performed on a 2010 EV mass spectrometer.

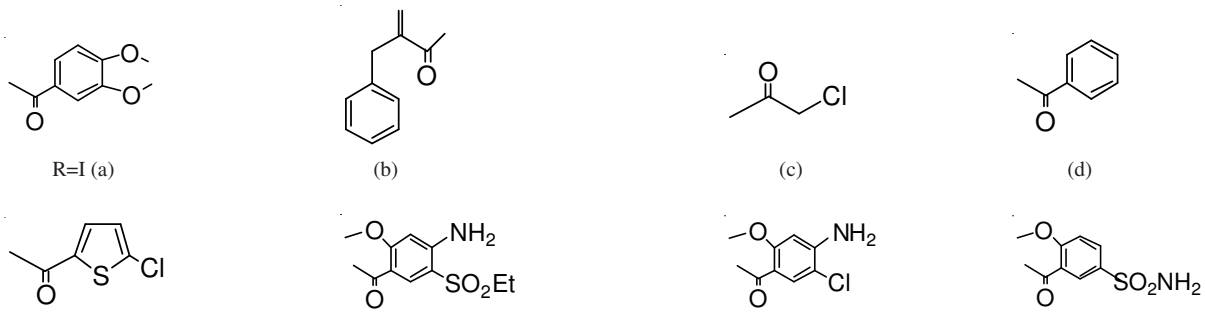
General procedure

Preparation of (S)-N-[[3-[3-fluoro-4-morpholin-4-yl-phenyl]-2-oxo-oxazolidin-5-yl methyl]-substituted amides 7(a-e): To a stirred solution of **6** (0.068 mol) in toluene (200 mL) was added triethylamine (0.102 mol) at room temperature. Then added slowly a solution of acid chlorides **I (a-e)** (0.10 mol) in toluene (50 mL) at 40-45 ºC and maintained at the



Scheme-I





Scheme-II

same temperature for 12 h (monitored by TLC). After completion, the reaction mixture was cooled to room temperature, solid was separated, filtered, washed with toluene (2 mL × 20 mL) and re-crystallized from methanol gave the compounds **7 (a-e)**.

Preparation of (S)-N-[[3-[3-fluoro-4-morpholin-4-yl-phenyl]-2-oxo-oxazolidin-5-yl methyl]-substituted benzamides 7(f-h): To a stirred mixture of **I (f-h)** (0.112 mol) in dichloromethane (200 mL) was added triethylamine (0.153 mol) at room temperature. The reaction mixture was cooled to 0-5 ºC added ethylchloroformate (0.123 mol) and maintained at 0.5 h, then added slowly a solution of **6** (0.102 mol) in dichloromethane (100 mL) at 0-5 ºC maintained at the same temperature for 3 h and stirred at room temperature for 1 h (monitored by TLC). After completion, the reaction mixture was washed with water and solvent evaporated, the remaining residue was recrystallized from methanol gave the compounds **7(f-h)**.

7a: (S)-N-[[3-[3-Fluoro-4-morpholinphenyl]-2-oxooxazolidin-5-yl)methyl]-3,4-dimethoxy benzamide: m.p. 168-170 ºC; yield: 83 %; IR (KBr, ν_{max}, cm^{-1}): 3324 (N-H stretching), 1766, 1634 (C=O stretching), 1440 (N-H bending), ^{1}H NMR (DMSO-d_6) δ ppm: 8.77-8.81 (s, 1H, NH), 7.50-7.42 (m, 3H), 7.19-7.16 (m, 1H), 7.08-7.01 (m, 2H), 4.90-4.88 (s, 1H), 4.18-4.12 (s, 1H), 3.88 (t, 1H), 3.81 (s, 6H), 3.78-3.75 (t, 4H), 3.65 (s, 2H), 2.97-2.91 (t, 4H). ^{13}C NMR (DMSO-d_6) δ ppm: 166.54, 156.19, 154.12, 152.96, 151.40, 148.21, 135.59, 133.36, 126.22, 120.61, 111.22, 114.08, 110.85, 106.82, 106.48, 71.49, 66.16, 55.58, 50.70, 47.54, 42.37. MS: 460 (M^+ + H).

7b: 2-Benzyl-(S)-N-[[3-[3-fluoro-4-morpholinphenyl]-2-oxooxazolidin-5-yl methyl acrylamide: m.p. 126-128 ºC; yield: 54 %; IR (K Br, ν_{max}, cm^{-1}): 3307 (N-H stretching), 1728, 1656 (C=O stretching), ^{1}H NMR (DMSO-d_6) δ ppm: 8.43-8.39 (s, 1H, NH), 7.46-7.40 (m, 1H), 7.24-7.19 (dd, 2H), 7.15-7.06 (m, 5H), 5.69 (s, 1H), 5.28 (s, 1H), 4.68-4.73 (t, 1H), 4.02-3.96 (s, 1H), 3.72-3.75 (t, 4H), 3.60-3.65 (s, 1H), 3.56 (d, 2H), 3.42-3.45 (t, 2H),2.97-2.94 (m, 4H). ^{13}C NMR (DMSO-d_6) δ ppm: 168.21, 156.22, 154.02, 152.99,143.88, 138.93, 135.56, 133.49, 128.61, 128.23, 126.04, 119.62, 119.19, 114.00, 106.75, 106.40, 71.26, 66.18, 50.72, 41.21, 40.66, 37.82. MS: 440 (M^+ + H).

7c: 2-Chloro-(S)-N-[[3-[3-fluoro-4-morpholinphenyl]-2-oxooxazolidin-5-yl)methyl acetamide: m.p. 177-180 ºC; yield: 71 %; IR (KBr, ν_{max}, cm^{-1}): 3297 (N-H stretching), 1747, 1682 (C=O stretching), ^{1}H NMR (DMSO-d_6) δ ppm: 8.59-8.62 (t, 1H), 7.45-7.51 (dd, 1H), 7.16-7.19 (m, 1H), 7.03-7.09 (m, 1H), 4.72-4.77 (m, 1H), 4.06-4.12 (m, 3H), 3.68-3.73 (m, 5H), 3.45-3.49 (m, 2H), 2.95 (m, 4H). ^{13}C NMR (DMSO-d_6) δ ppm: 166.83, 156.18, 153.96, 135.50, 133.30, 119.15, 114.08, 106.52, 71.25, 66.15, 50.67, 47.23, 42.45, 41.81. MS: 372 (M^+ + H).

7d: (S)-N-[[3-[3-Fluoro-4-morpholinphenyl]-2-oxooxazolidin-5-yl)methyl]benzamide: m.p. 136-138 ºC; yield: 54 %; IR (KBr, ν_{max}, cm^{-1}): 3320 (N-H stretching), 1750, 1732 (C=O stretching), 1488 (N-H bending), ^{1}H NMR (DMSO-d_6) δ ppm: 8.82-8.85 (t, 1H), 7.83-7.85 (d, 2H), 7.44-7.54 (m, 4H), 7.18-7.20 (m, 1H),7.02-7.08 (m, 1H), 4.83-4.87 (m, 1H), 4.18-3.82 (m, 2H), 3.73 (m, 4H), 3.61-3.63 (m, 2H), 2.95 (m, 4H). ^{13}C NMR (DMSO-d_6) δ ppm: 167.07, 156.22, 154.12, 135.48, 133.37, 131.41, 128.30, 127.32, 119.15, 114.07, 106.48, 71.36, 66.17, 50.70, 47.57, 42.34. MS: 422 (M^+ + H).

7e: (S)-5-Chloro-N-[[3-[3-fluoro-4-morpholinphenyl]-2-oxooxazolidin-5-yl)methyl] thiophen-2-carboxamide: m.p. 194-197 ºC; tield: 87 %; IR (KBr, ν_{max}, cm^{-1}): 3352, 3336 (N-H stretching), 1745, 1719, 1634 (C=O stretching); ^{1}H NMR (DMSO-d_6) δ ppm: 8.94-8.98 (s, 1H), 7.62-7.69 (d, 1H), 7.44-7.50 (dd, 1H), 7.16-7.20 (m, 2H), 7.02-7.08 (t, 1H), 4.77-4.86 (m, 1H), 4.10-4.16 (t, 2H), 3.76-3.81 (m, 1H), 3.71-3.74 (t, 4H), 3.57-3.60 (t, 2H), 2.94-2.96 (t, 4H). ^{13}C NMR (DMSO-d_6) δ ppm: 160.81, 156.17, 138.31, 135.46, 133.31, 128.40, 128.02, 119.08, 114.02, 106.46, 71.35, 66.14, 50.65, 47.47, 42.21. MS: 439.91 (M^+ + H).

7f: 4-Amino-(ethylsulfonyl)-N-(S)-[[3-[3-fluoro-4-morpholinphenyl]-2-oxooxazolidin-5-yl)methyl]-2-methoxy benzamide: m.p. 185-187 ºC; yield: 93 %; IR (KBr, ν_{max}, cm^{-1}): 3450, 3407 (N-H stretching), 1748, 1652, 1638 (C=O stretching). ^{1}H NMR (DMSO-d_6) δ ppm: 8.20-8.17 (s,1H, NH), 8.06.(s, 1H), 7.51-7.45 (dd, 1H), 7.19-7.16 (m, 1H), 7.08-7.01 (m, 1H), 6.53 (br, 2H, -NH_2), 6.48 (s, 1H), 4.82-4.87 (q, 1H), 4.09-4.15 (t, 1H), 3.79-3.83 (s, 3H), 3.71-3.74 (s, 1H), 3.61-3.62 (m, 4H), 3.40-3.30 (dd, 2H), 3.11-3.18 (t, 2H), 2.93-2.96 (m, 4H), 1.05-1.10 (t, 3H). ^{13}C NMR (DMSO-d_6) δ ppm: 164.19, 161.95, 156.18, 154.08, 152.95, 151.52, 135.58, 134.96, 133.45, 119.18, 114.05, 110.65, 110.33, 106.79, 98.09, 71.40, 66.15, 56.08, 50.68, 48.36, 47.45, 42.11, 7.06. MS: 535 (M^+ + H).

7g: 4-Amino-5-chloro-2-ethoxy-N-(S)-[[3-[3-fluoro-4-morpholinphenyl]-2-oxooxazolidin-5-yl)methyl]-benzamide: m.p. 221-222 ºC; yield: 70 %; IR (KBr, ν_{max}, cm^{-1}): 3472,3374 (N-H stretching), 1760, 1644 (C=O stretching). ^{1}H NMR (DMSO-d_6) δ ppm: 8.16-8.12 (br, 1H,), 7.67(s, 1H), 7.44-7.50 (dd, 1H), 7.18-7.14 (dd, 1H), 7.01-7.07 (dd, 1H), 6.45 (s, 1H), 5.99 (br, 2H, NH_2), 4.81-4.85 (m, 1H), 4.02-4.12 (m, 3H), 3.70-3.73 (m, 5H), 3.64-3.68 (t, 2H), 2.92-2.95 (t, 4H), 1.35-1.40 (t, 3H). ^{13}C NMR (DMSO-d_6) δ ppm: 164.34, 156.30, 156.16, 153.97, 152.93, 148.72, 135.59, 133.42, 131.58, 119.10, 114.05, 109.85, 109.01, 106.78, 98.21, 71.64, 66.13, 64.45, 50.67, 47.32, 41.58,14.29. MS: 492 (M^+ + H).

7h: 5-(-Aminosulpfonyl)-N-(S)-[[3-[3-fluoro-4-morpholinphenyl]-2-oxooxazolidin-5-yl)methyl]-2-methoxy benzamide: m.p. 161-163 ºC; yield: 55 %; IR (KBr, ν_{max}, cm^{-1}): 3383, 3292 (N-H stretching), 1755 (C=O stretching), 1227 (SO_2 stretching). ^{1}H NMR (DMSO-d_6) δ ppm: 8.57-8.60 (t, 1H), 8.13 (s, 1H), 7.86-7.89 (d, 1H), 7.47-7.52 (dd, 1H), 7.26-7.32 (dd, 2H), 7.17-7.19 (m, 1H), 7.08 (m, 1H), 7.02-7.05 (m, 1H), 4.86 (m, 1H), 4.11-4.17 (t, 1H), 3.86 (s, 3H), 3.80 (m, 1H), 3.72 (m, 4H), 3.62-3.67 (m, 2H), 2.94 (m, 4H). ^{13}C NMR (DMSO-d_6) δ ppm: 164.82, 156.22, 154.12, 136.23, 135.52, 129.93, 128.30, 123.11, 119.30, 114.11, 112.42, 106.83, 71.29, 66.19, 56.50, 50.73, 47.37, 42.08. MS: 501 (M^+ + H).

RESULTS AND DISCUSSION

Compounds **7(a-h)** were initially screened for *in vitro* antibacterial activity against gram positive bacterial strains *Staphylococcus aureus*, *Staphylococcus citreus* and gram negative bacterial strains *Proteus vulgaris*m, *Salmonella typhimurium*, *Klebsiella pneumonia* utilizing the agar diffusion assay. The antibacterial screening for analogs and positive control was performed at a fixed concentration of 1000 µg/mL. All the eight compounds in Table-1 exhibit antibacterial activity against both gram positive and gram negative bacterial strains with zones of inhibition (ZOI) ranging from 0.3-2.0 cm. Compounds **7c** and **7d** were identified as good antibacterial agent against all gram positive and gram negative bacterial strains. Compounds **7a**, **7b** and **7e** showed moderate activity and **7g** inactive against all gram positive and gram negative bacterial strains.

TABLE-1
ZONE OF INHIBITION OF DATA FOR LINZOLID ANALOGS **7(a-h)** AGAINST DIFFERENT BACTERIA AT 1000 µg/mL CONCENTRATION

Analogs	Zone of Inhibition (in cm)				
	Bacteria[a]		Bacteria[b]		
	SC	SA	PV	ST	KP
7a	0.6	0.5	0.6	0.5	0.5
7b	0.9	0.7	0.7	0.4	0.3
7c	1.3	2.0	1.5	1.5	1.0
7d	1.2	1.0	1.0	1.2	1.0
7e	0.8	0.5	0.6	0.3	1.0
7f	–	–	0.2	0.2	–
7g	–	–	–	–	–
7h	–	–	0.4	0.3	0.3
Linzolid	2.3	2.5	2.0	2.0	2.2

[a]Gram positive bacteria: SG: *Staphylococcus citreus*, SA: *Staphylococcus aureus*. [b]Gram negative bacteria: PV: *Proteus vulgarism*, ST: *Salmonella typhimurium*, KP: *Klebsiella pneumonia*.

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